Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial

Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial

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Summary

Background Previous studies suggested intravenous or nebulised magnesium sulphate ($MgSO_4$) might improve respiratory function in patients with acute asthma. We aimed to determine whether intravenous or nebulised $MgSO_4$ improve symptoms of breathlessness and reduce the need for hospital admission in adults with severe acute asthma.

Methods In our double-blind, placebo-controlled trial, we enrolled adults (aged ≥16 years) with severe acute asthma at emergency departments of 34 hospitals in the UK. We excluded patients with life-threatening features or contraindication to study drugs. We used a central randomisation system to allocate participants to intravenous $MgSO_4$ (2 g in 20 min) or nebulised $MgSO_4$ (three 500 mg doses in 1 h) alongside standard therapy including salbutamol, or placebo control plus standard therapy alone. We assessed two primary outcome measures in all eligible participants who started treatment, according to assigned treatment group: the proportion of patients admitted to hospital within 7 days and breathlessness measured on a 100 mm visual analogue scale (VAS) in the 2 h after initiation of treatment. We adjusted for multiple testing using Simes's method. The trial stopped before recruitment was completed because funding expired. This study is registered, number ISRCTN04417063.

Findings Between July 30, 2008, and June 30, 2012, we recruited 1109 (92%) of 1200 patients proposed by the power calculation. 261 (79%) of 332 patients allocated nebulised $MgSO_4$ were admitted to hospital before 7 days, as were 285 (72%) of 394 patients allocated intravenous $MgSO_4$ and 281 (78%) of 358 controls. Breathlessness was assessed in 296 (89%) patients allocated nebulised $MgSO_4$, 357 (91%) patients allocated intravenous $MgSO_4$, and 323 (90%) controls. Rates of hospital admission did not differ between patients treated with either form of $MgSO_4$ compared with controls or between those treated with nebulised $MgSO_4$ and intravenous $MgSO_4$. Change in VAS breathlessness did not differ between active treatments and control, but change in VAS was greater for patients in the intravenous $MgSO_4$ group than it was in the nebulised $MgSO_4$ group (5·1 mm, 0·8 to 9·4; p=0·019). Intravenous or nebulised $MgSO_4$ did not significantly decrease rates of hospital admission and breathlessness compared with placebo: intravenous $MgSO_4$ was associated with an odds ratio of 0·73 (95% CI 0·51 to 1·04; p=0·083) for hospital admission and a change in VAS breathlessness of 2·6 mm (–1·6 to 6·8; p=0·231) compared with placebo; nebulised $MgSO_4$ was associated with an odds ratio of 0·96 (0·65 to 1·40; p=0·819) for hospital admission and a change in VAS breathlessness of –2·6 mm (–7·0 to 1·8; p=0·253) compared with placebo.

Interpretation Our findings suggest nebulised $MgSO_4$ has no role in the management of severe acute asthma in adults and at best suggest only a limited role for intravenous $MgSO_4$ in this setting.

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See Online for appendix

Introduction

Acute asthma leads to about 60 000 hospital admissions per year in England.[1] Present guidelines[2,3] advise a stepwise approach to the management of exacerbations. Initially, all patients should receive oxygen, nebulised β_2 agonists, a nebulised anticholinergic drug, and corticosteroids. However, bronchodilators act within minutes whereas corticosteroids require hours to take effect. This difference suggests a potential role for magnesium sulphate ($MgSO_4$) as an additional treatment option in the therapeutic gap between nebulised bronchodilators and corticosteroids.

$MgSO_4$ has been assessed in intravenous and nebulised forms. The nebulised route offers the potential advantage of a quick onset of action and reduced incidence of side-effects. Its disadvantages include a reduced dose of drug delivered compared with the intravenous form and respiratory effort on the part of the patient to increase its effectiveness. The intravenous route provides direct access to the venous system, allowing the delivery of high drug concentrations. Disadvantages include the need for intravenous access and drug administration by infusion lasting about 20 min.

Several systematic reviews and meta-analyses have assessed the role of intravenous or nebulised $MgSO_4$ in acute asthma.[4–10] The most recent review[10] suggested that intravenous treatment seemed effective in children but was unable to draw clear conclusions about treatment in adults. Both intravenous treatment (assessed in ten trials, with 955 adults) and nebulised treatment (seven trials,

430 adults) were associated with weak evidence of improved respiratory function compared with control populations all treated with standard care. No trials directly compared intravenous $MgSO_4$ with nebulised $MgSO_4$. The standardised mean difference (SMD) in respiratory function for intravenous treatment was 0·25 (95% CI –0·01 to 0·51; p=0·06) and for nebulised treatment was 0·17 (95% CI –0·02 to 0·36; p=0·09). Meta-analysis showed that intravenous treatment was associated with weak evidence of an effect on hospital admission (relative risk [RR] 0·68, 95% CI 0·46 to 1·02; p=0·06), whereas nebulised treatment was associated with no significant effect (0·87, 0·70 to 1·08; p=0·22) compared with standard care. One further trial of intravenous $MgSO_4$ in adults[11] has since been published. Inclusion of this trial in the meta-analysis[12] resulted in a slightly larger and significant effect on respiratory function (SMD 0·35, 95% CI 0·06 to 0·64; p=0·02) but the effect on hospital admission remained non-significant (RR 0·85, 95% CI 0·68 to 1·06; p=0·14). Whether changes in measures of respiratory function were associated with important changes in management of patients or a clinically meaningful improvement in symptoms was unclear.

Uncertainty in the evidence is shown in treatment recommendations. Current guidelines in the UK[2] and the USA[3] suggest that intravenous $MgSO_4$ should be considered in adults with life-threatening features or severe acute asthma that has not responded to inhaled bronchodilator therapy. No recommendations are made regarding nebulised $MgSO_4$.

We aimed to assess the effectiveness of intravenous and nebulised $MgSO_4$ in adults with severe acute asthma. We specifically aimed to determine whether intravenous or nebulised $MgSO_4$, used alongside standard treatment including salbutamol, reduces the proportion of patients requiring hospital admission at initial presentation or during the subsequent 7 days, and whether intravenous or nebulised $MgSO_4$ improves patient-assessed levels of breathlessness up to 2 h after the start of treatment.

For the **trial protocol** see http://www.thelancet.com/protocol-reviews/08PRT-503

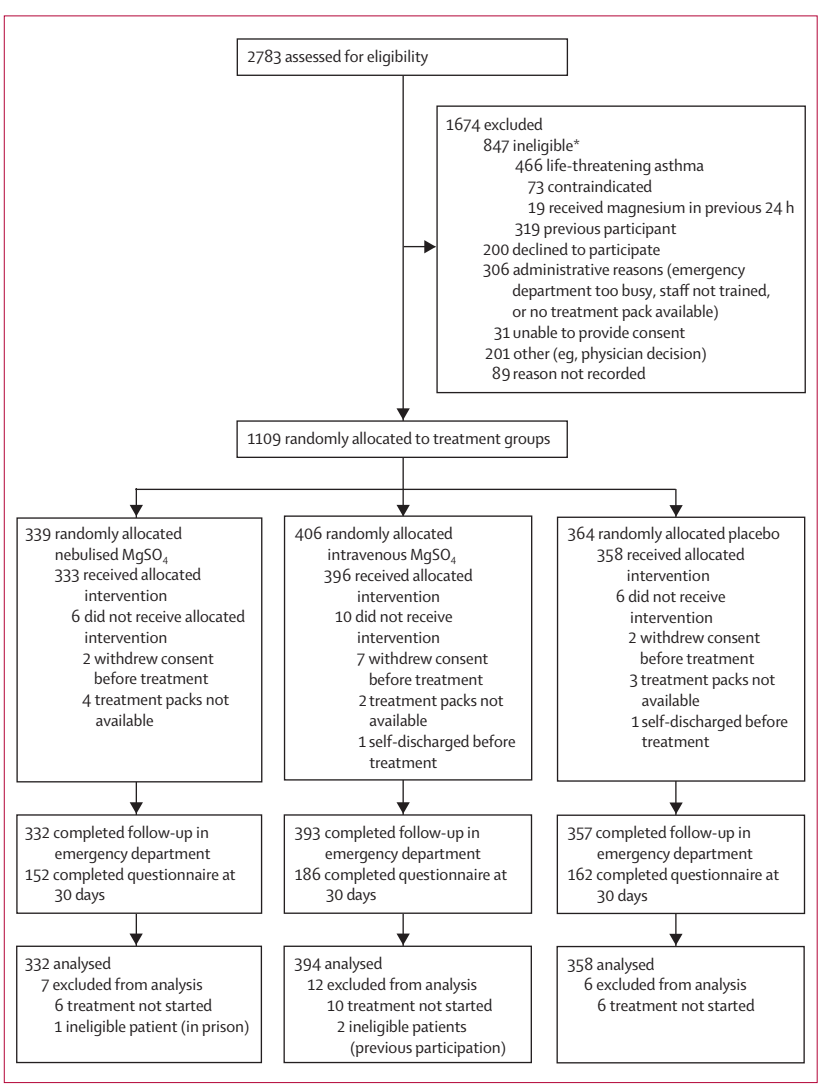

Figure 1: **Study profile**
*Patients could meet ≥1 exclusion criteria.

Methods

Study design and patients

We undertook a multicentre, double-blind, placebo-controlled, three-arm, randomised trial at 34 emergency departments in the UK. The trial protocol was published previously.

Eligible patients were adults (aged ≥16 years) attending an emergency department with severe acute asthma (ie, acute asthma with either a peak expiratory flow rate of <50% of best or predicted, respiratory rate >25 breaths per min, heart rate >110 beats per min, or inability to complete sentences in one breath). We excluded patients who had life-threatening features (oxygen saturation <92%, silent chest, cyanosis, poor respiratory effort, bradycardia, arrhythmia, hypotension, exhaustion, coma, or confusion), a contraindication to either nebulised or intravenous $MgSO_4$ (pregnancy, hepatic or renal failure, heart block, or known hypermagnesaemia), individuals who were unable to provide written or verbal consent, and previous participants in the 3Mg trial. We amended the protocol during the trial to also exclude individuals who had received $MgSO_4$ in the 24 h before recruitment. We sought written or verbal consent from all participants. Patients who initially provided verbal consent were asked for written consent as soon as their condition permitted.

An independent data monitoring committee reviewed trial data at regular intervals and reported recommendations to the trial steering committee in accordance with the data monitoring committee charter. The trial was approved by the Scotland A Research Ethics Committee.

Randomisation and masking

We randomly allocated participants with a telephone or internet randomisation system, which was managed by

the Sheffield Clinical Trials Research Unit (CTRU). After entry into the trial, participants were allocated to numbered treatment packs kept in the emergency department. We used a simple randomisation sequence in the first 20 participating hospitals, but switched to blocked randomisation (block sizes of four or six), stratified by hospital, for subsequent hospitals to safeguard against new centres recruiting too few participants in any trial arm. Every treatment pack contained an intravenous infusion and three nebuliser solutions, either of which could be active treatment or placebo. Participants, hospital staff, and research staff were masked to allocated treatment.

Procedures

Patients were allocated to receive one of three treatments: intravenous $MgSO_4$ (8 mmol [2 g] in 100 mL normal saline provided over 20 min) and three 7·5 mL vials of 0·9% saline nebulised at 20 min intervals (intravenous $MgSO_4$ group); intravenous normal saline (100 mL given over 20 min) and three 7·5 mL vials of 2 mmol (500 mg) $MgSO_4$ nebulised at 20 min intervals (nebulised $MgSO_4$ group); or intravenous normal saline (100 mL given over 20 min) and three 7·5 mL vials of 0·9% saline nebulised at 20 min intervals (placebo group).

Patients received standard therapy in accordance with guidelines[2] from the British Thoracic Society and Scottish Intercollegiate Guidelines Network and consisted of oxygen, nebulised salbutamol (5 mg), nebulised ipratropium (500 µg), and oral prednisolone administered during recruitment, followed by up to 5 mg salbutamol added to each trial nebuliser. Other treatments were provided at the discretion of the clinician. Patients were managed in the emergency department and data were collected until 2 h after randomisation. At this point, if not already undertaken, a final disposition decision was made (hospital admission or discharge) and initial data collection was completed.

We prespecified two primary outcomes. The first was a health service primary outcome, defined as the proportion of patients admitted to hospital, either after emergency department treatment or at any time in the subsequent 7 days. The second was a patient-centred primary outcome, defined as the patient's visual analogue scale (VAS) for breathlessness in the 2 h after start of treatment. VAS breathlessness has been used to measure breathlessness during exercise[13] and has been shown to correlate with respiratory function and symptomatic change in cohorts with acute asthma.[14,15]

Secondary outcomes included mortality, adverse events, use of ventilation or respiratory support, length of hospital stay, admission to a high-dependency unit or intensive-care unit, change in peak expiratory flow rate and physiological variables (oxygen saturation, heart rate, respiratory rate, blood pressure) over 2 h, change in quality of life between baseline and 1 month, number of unscheduled health-care contacts over the subsequent month, and satisfaction with care (these outcomes will be reported elsewhere).

Treating clinicians routinely recorded adverse events and side-effects occurring during emergency department treatment on case report forms. Key events (cardiac arrest, respiratory arrest, emergency intubation, non-invasive ventilation, pneumothorax, and arrhythmia)

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)	Overall (n=1084)
Age, years				
Mean	36·5 (14·8)	35·6 (13·1)	36·4 (14·1)	36·1 (14·0)
Median	35·0 (23·0–47·0)	34·0 (25·0–44·0)	34·5 (24·0–47·0)	34·0 (24·0–46·0)
Range	16–85	16–84	16–88	16–88
Sex, female	232 (70%)	279 (71%)	252 (70%)	763 (70%)
Ethnic group				
White	286 (86%)	369 (94%)	319 (89%)	974 (90%)
Mixed	2 (1%)	1 (<1%)	5 (1%)	8 (1%)
Asian or Asian British	14 (4%)	8 (2%)	16 (4%)	38 (4%)
Black or black British	2 (1%)	5 (1%)	4 (1%)	11 (1%)
Other	2 (1%)	0	0	2 (<1%)
Not stated	22 (7%)	8 (2%)	11 (3%)	41 (4%)
Missing	4 (1%)	3 (1%)	3 (1%)	10 (1%)
Smoking status				
Never	151 (45%)	156 (40%)	143 (40%)	450 (42%)
Current	98 (30%)	138 (35%)	127 (35%)	363 (33%)
Previous	72 (22%)	95 (24%)	81 (23%)	248 (23%)
Missing data	11 (3%)	5 (1%)	7 (2%)	23 (2%)
Predicted peak expiratory flow rate, L per min				
Data available	324	389	346	1059
Mean	430·0 (118·8)	431·8 (116·9)	435·0 (110·8)	432·3 (115·4)
Median	425·0 (350·0–500·0)	435·0 (350·0–500·0)	425·0 (350·0–500·0)	425·0 (350·0–500·0)
Range	100–700	140–800	150–790	100–800
Other previous serious lung disease	29 (9%)	42 (11%)	27 (8%)	98 (9%)
Other serious illness	69 (21%)	66 (17%)	68 (19%)	203 (19%)

Data are mean (SD), median (IQR), or n (%), unless otherwise stated.

Table 1: **Baseline characteristics**

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)	Overall (n=1084)
Status at 4 h				
Admitted	254 (77%)	279 (71%)	278 (78%)	811 (75%)
Discharged	77 (23%)	114 (29%)	80 (22%)	271 (25%)
Died	0	0	0	0
Unknown	1 (<1%)	1 (<1%)	0	2 (<1%)
Subsequent hospital admission within 7 days	15 (5%)	10 (3%)	7 (2%)	32 (3%)
Subsequent hospital admission after discharge at initial attendance	6 (2%)	5 (1%)	3 (1%)	14 (1%)
Admitted to hospital at any time within 7 days	261 (79%)	285 (72%)	281 (78%)	827 (76%)

Data are n (%).

Table 2: **Admission to hospital**

and common side-effects (flushing, nausea, vomiting, and hypotension [systolic pressure <100 mm Hg]) were specifically sought and recorded. Other events were recorded on a general adverse event reporting form. A research nurse reviewed patient notes and recorded any side-effects identified during treatment or adverse events occurring up to 30 days after treatment. We identified adverse events and reported them according to good clinical practice guidance.

Statistical analysis

We planned to recruit 1200 participants (400 patients per group). Assuming 80% of patients with severe acute asthma were admitted after emergency department management and hospital admission is recorded for all participants, the study would have 90% power to detect a 10% absolute reduction in the proportion admitted (ie, to 70%) for any pair of treatment groups compared (two-sided α=0·05). Assuming 80% of participants had a VAS measurement, then the study would have 90% power to detect an 8 mm difference in a 100 mm VAS at 2 h after treatment initiation (two-sided α=0·05). Previous data have established that the standard deviation on a 100 mm VAS is 30 mm, and that 22 mm represents a minimum clinically significant difference.[14]

We analysed participants in the groups to which they were allocated, irrespective of whether they actually received or completed the allocated treatment. We used logistic regression for analysis of admission rates. For length of stay, we compared means with censored normal regression and medians with log-normal regression to account for interval censoring in discharged patients (for whom no time of discharge was recorded) and also admissions that were ongoing at 30 days. We compared the number of days spent in the intensive-care unit or high-dependency unit with the Mann-Whitney *U* test. We used ANCOVA for assessment of all other outcomes. We assessed the primary outcome in all eligible patients who started treatment, adjusted for hospital of admission. We also did additional analyses with different imputation strategies as confirmatory analyses. We did a secondary explanatory analysis restricted to individuals who completed the treatment as per protocol. We used Simes's method,[16] which is a modification of the Bonferroni method with increased power, to adjust for multiplicity arising from use of two primary outcomes. The two preplanned comparisons between the three groups were active treatment (intravenous or nebulised) versus placebo and intravenous $MgSO_4$ versus nebulised $MgSO_4$. We also present comparisons of intravenous $MgSO_4$ versus placebo and nebulised $MgSO_4$ versus placebo for completeness. We undertook three preplanned subgroup analyses assessing the primary outcomes (hospital admission and VAS breathlessness) between active and placebo groups stratified by age (≥50 years *vs* <50 years), baseline peak expiratory flow rate (less than median *vs* median or greater), and previous treatment with salbutamol before the trial treatments (yes *vs* no).

This study is registered, number ISRCTN04417063.

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)
VAS at baseline			
Patients assessed	326 (98%)	386 (98%)	349 (97%)
Mean, mm	61·6 (23·3)	61·9 (22·8)	63·1 (23·5)
Change in VAS at 1 h			
Patients assessed	314 (95%)	372 (94%)	344 (96%)
Mean change, mm	−18·4 (22·8)	−24·2 (24·4)	−21·5 (24·7)
Change in VAS at 2 h			
Patients assessed	296 (89%)	357 (91%)	323 (90%)
Mean change, mm	−28·2 (27·4)	−34·3 (27·7)	−31·3 (29·4)

Data are n (%) or mean (SD). VAS=visual analogue scale.

Table 3: **Change in VAS breathlessness**

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)
Percentage predicted PEFR at baseline			
Patients assessed	308 (93%)	375 (95%)	327 (91%)
Mean	50·0% (19·6)	54·3% (20·2)	50·5% (19·1)
Change in percentage PEFR at 1 h			
Patients assessed	282 (85%)	349 (89%)	304 (85%)
Mean	9·9% (15·0)	11·4% (15·7)	10·2% (14·7)
Change in percentage PEFR at 2 h			
Patients assessed	270 (81%)	337 (86%)	291 (81%)
Mean	13·4% (18·0)	14·4% (17·4)	14·4% (16·3)

Data are n (%) or mean (SD). PEFR=peak expiratory flow rate.

Table 4: **Change in percentage of predicted PEFR**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited patients at 34 hospitals between July 30, 2008, and June 30, 2012. Recruitment was slower than anticipated and ended when the trial funding expired after 1109 patients eligible for random allocation had been enrolled (figure 1). Of these 1109 patients, 25 withdrew without starting trial drug, were recruited in error (protocol violations), or could not be allocated to a treatment pack, leaving 1084 patients included in the analysis. Table 1 shows the baseline characteristics. Age and sex characteristics were balanced across the groups, but there were more white patients in the intravenous magnesium group and more patients who had never

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)	p values	
				Active *vs* placebo	Intravenous *vs* nebulised $MgSO_4$
Length of stay, h					
Data available	329 (99%)	388 (98%)	353 (99%)		
Mean	63·2 (79·7)	57·0 (75·1)	63·3 (84·3)	0·659	0·379
Median	35·1 (4·5–88·7)	31·5 (4·0–78·4)	36·4 (4·5–87·3)	0·432	0·230
Range	3–623	4–723	1–694		
Days in an intensive-care unit					
Patients with any stay	9 (3%)	11 (3%)	5 (1%)	0·161	0·947
Mean	3·3 (4·8)	3·1 (5·0)	2·9 (3·9)		
Median	2·0 (1–4)	2·0 (0–4)	2·0 (0–4)	0·159	0·941
Days in a high-dependency unit					
Patients with any stay	22 (7%)	23 (6%)	20 (6%)	0·690	0·661
Mean	3·3 (4·8)	3·1 (5·0)	2·9 (3·9)		
Median	2·0 (1–4)	2·0 (0–4)	2·0 (0–4)	0·715	0·630
Required ventilation	3 (1%)	6 (2%)	4 (1%)	0·936	0·458
Non-invasive	2 (1%)	2 (1%)	3 (1%)		
Emergency intubation	2 (1%)	4 (1%)	1 (<1%)		

Data are n (%), mean (SD), or median (IQR), unless otherwise stated.

Table 5: **Length of stay, intensive-care unit and high-dependency unit admission, and use of ventilation**

smoked in the nebulised magnesium group. The appendix shows the trial drugs received by the three groups of patients and concurrent treatments. The mean overall dose of nebulised solution was 21·3 mL (SD 3·9), with 917 (85%) of 1084 patients receiving the full dose of 22·5 mL, and the mean total dose of intravenous infusion was 97·1 mL (SD 14·6) with 968 (89%) receiving the full intravenous infusion.

Table 2 and table 3 show the results of the primary outcome analysis. Rates of admission to hospital did not differ between groups for comparisons of active treatment and placebo (odds ratio 0·84, 95% CI 0·61–1·15; p=0·276), intravenous $MgSO_4$ and nebulised $MgSO_4$ (0·76, 0·53–1·10; p=0·146), intravenous $MgSO_4$ and placebo (0·73, 0·51–1·04; p=0·083), or nebulised $MgSO_4$ and placebo (0·96, 0·65–1·40; p=0·819; table 2). Mean improvements in VAS (a positive value shows a greater improvement than in the comparator) did not differ between groups for comparisons of active treatment and placebo (0·0 mm, 95% CI –1·9 to 1·9; p=0·999), intravenous $MgSO_4$ versus placebo (2·6 mm, –1·6 to 6·8; p=0·231), and nebulised $MgSO_4$ versus placebo (–2·6 mm, –7·0 to 1·8; p=0·253), but the change in VAS was greater for patients in the intravenous $MgSO_4$ group than it was in the nebulised $MgSO_4$ group (5·1 mm, 0·8 to 9·4; p=0·019; table 3). Further analyses were run with plausible imputations for the 108 (10%) patients with no 2 h change in VAS recorded; these analyses had no material effect on the findings (data not shown).

Table 4 shows the analysis of peak expiratory flow rate as a percentage of the predicted rate. The mean differences in improvement in percentage predicted peak expiratory flow rate at 2 h were –0·5% (95% CI –2·9 to 1·9; p=0·676) for active treatment versus placebo, 0·3% (–2·4 to 3·0; p=0·841) for intravenous $MgSO_4$ versus nebulised $MgSO_4$, –0·4% (–3·0 to 2·3; p=0·786) for intravenous $MgSO_4$ versus placebo, and –0·6% (–3·4 to 2·1; p=0·652) for nebulised $MgSO_4$ versus placebo (a positive value shows a greater improvement than in the comparator). Comparison of physiological measures identified no differences between groups. Full details of physiological measures and oxygen flow rates are provided in the appendix.

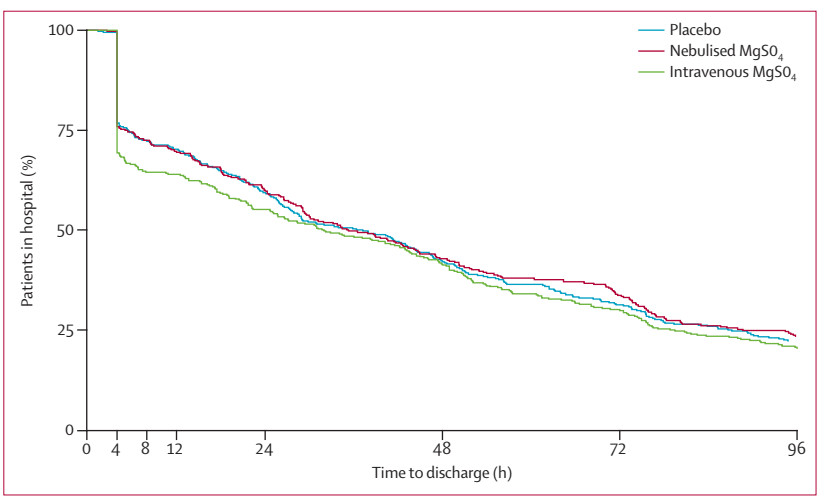

Figure 2: **Length of stay after initial hospital attendance**

Length of stay, rates of admission to the intensive-care unit or high-dependency unit, and use of respiratory support did not differ between groups (table 5). Figure 2 shows the proportion of patients in hospital by treatment group as a function of time from hospital admission. Any small difference between the groups had disappeared by 24 h.

Table 6 shows adverse events and side-effects. Incidence of side-effects was increased in patients who received active treatment compared with placebo (odds ratio 1·68, 95% CI 1·11–2·52; p=0·014) and the subgroups of intravenous $MgSO_4$ compared with placebo (1·68, 1·07–2·63; p=0·025) and nebulised $MgSO_4$ compared with placebo 1·67 (1·05–2·66, p=0·031), but we noted no differences between intravenous $MgSO_4$ and nebulised $MgSO_4$ (1·00, 0·66–1·52; p=0·988). Table 7 shows the drugs prescribed to patients discharged after emergency department treatment. 218 (80%) of 271 patients discharged at 4 h received prednisolone and 100 (37%) received additional inhalers.

We noted no significant differences on pre-planned subgroup analysis. Rates of hospital admission with intravenous $MgSO_4$ did not differ from placebo (odds ratio 0·76, 95% CI 0·45–1·30; p=0·332) in patients presenting with more severe asthma (defined as median peak expiratory flow rate or lower) or in individuals presenting with less severe asthma (0·67, 0·42–1·06; p=0·088). Data for rates of hospital admission split by age group and previous salbutamol treatment will be reported elsewhere.

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)	Overall (n=1084)
Adverse events				
Any adverse events	41 (12%)	53 (13%)	36 (10%)	130 (12%)
Arrhythmia	0	1 (<1%)	1 (<1%)	2 (<1%)
Cardiac arrest	0	1 (<1%)	0	1 (<1%)
Death	1 (<1%)	1 (<1%)	0	2 (<1%)
Intubation	2 (1%)	4 (1%)	1 (<1%)	7 (1%)
Non-invasive ventilation	2 (1%)	2 (1%)	3 (1%)	7 (1%)
Other (asthma related)	26 (8%)	26 (7%)	22 (6%)	74 (7%)
Other (non-asthma related)	14 (4%)	20 (5%)	12 (3%)	46 (4%)
Side-effects				
Any side-effect	52 (16%)	61 (15%)	36 (10%)	149 (14%)
Flushing	3 (1%)	7 (2%)	2 (1%)	12 (1%)
Hypotension	31 (9%)	31 (8%)	22 (6%)	84 (8%)
Nausea	5 (2%)	14 (4%)	7 (2%)	26 (2%)
Vomiting	6 (2%)	6 (2%)	3 (1%)	15 (1%)
Other	12 (4%)	15 (4%)	5 (1%)	32 (3%)

Total number of events will not equal the sum of individual events if a patient has more than one side-effect.

Table 6: **Adverse events and side-effects**

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=394)	Placebo (n=358)
Discharged at 4 h	77 (23%)	114 (29%)	80 (22%)
Any drug	64 (83%)	98 (86%)	64 (80%)
Prednisolone	62 (81%)	93 (82%)	63 (79%)
Salbutamol	21 (27%)	44 (39%)	27 (34%)
Fluticasone-salmeterol	3 (4%)	4 (4%)	2 (3%)
Beclometasone	1 (1%)	4 (4%)	3 (4%)
Budesonide	3 (4%)	3 (3%)	0
Ipratropium	1 (1%)	1 (1%)	0
Salmetarol	0	1 (1%)	0
Ipratropium-salbutamol	1 (1%)	0	0
Other	0	2 (2%)	0

Table 7: **Drugs provided at discharge at 4 h**

Discussion

To our knowledge, the 3Mg trial is the largest trial of $MgSO_4$ undertaken in acute asthma, the first trial powered to detect a meaningful difference in rates of admission to hospital, and the first to directly compare intravenous treatment with nebulised treatment (panel). We did not show a clinically meaningful benefit from either intravenous or nebulised $MgSO_4$ compared with placebo. Intravenous $MgSO_4$ might have an effect on rates of hospital admission and the confidence interval for this estimate included the possibility of both a worthwhile effect and no effect, but any effect we noted on breathlessness was smaller than the minimum clinically significant difference.[13] We noted no suggestion of an effect from nebulised $MgSO_4$ in either primary outcome.

Meta-analysis of previous trials suggested evidence of benefit from intravenous and nebulised $MgSO_4$.[10] This suggestion contrasts with our findings of no benefit from nebulised treatment and weak evidence of benefit from intravenous treatment. Several factors might explain this inconsistency. Meta-analysis can be subject to publication bias if positive trials are preferentially submitted and accepted for publication. Some previous trials might have been restricted by inadequate allocation concealment or masking that inflated estimates of treatment effects. Patients in all three arms of the 3Mg trial received treatment with nebulised β agonists which might have restricted the ability of $MgSO_4$ to provide additional bronchodilation, whereas it was not always clear that all patients received optimum standard treatment in previous trials. Notably, patients in the control group of 3Mg had improvements in peak expiratory flow rate and VAS breathlessness, and few required respiratory support, suggesting a good response to standard treatment alone.

One potential explanation that can probably be discounted is that the 3Mg trial treatment was inadequate, in terms of the planned dose and actual amount of drug given. The protocol-specified doses of intravenous and nebulised $MgSO_4$ were at the top end of doses used in previous trials, and most patients received the full dose

of the relevant drugs (appendix). Pragmatic trials carry a risk that trial treatment will be delivered in a suboptimal manner, but we noted no evidence of this in the 3Mg trial.

Our findings for nebulised $MgSO_4$ contrast with those of the MAGNETIC trial,[17] which showed an improvement in asthma severity score at 60 min after treatment with nebulised $MgSO_4$ compared with placebo in children and adolescents with acute severe asthma.[17] Previous meta-analysis[10] suggested that intravenous $MgSO_4$ is more effective in children than adults. Findings from 3Mg and MAGNETIC suggest that the same is true of nebulised $MgSO_4$.

The 3Mg trial had some limitations. The trial terminated when funding expired and had recruited 1109 patients (92%) of a target of 1200. Despite this shortfall, the trial had 84% power to detect a 10% difference in admission rate for nebulised treatment versus placebo and 87% power for intravenous $MgSO_4$ versus placebo based on the original sample-size projections. Furthermore, VAS breathlessness was recorded for 90% of the study population, as opposed to the anticipated 80% in the power calculation, so there was no loss of power to detect a difference in this outcome.

3Mg was designed as a pragmatic trial to determine the effectiveness of use of $MgSO_4$ alongside other treatments as part of routine emergency department practice. The study population was pragmatically defined by use of information routinely available to emergency department staff. Thus, findings should be generalisable to typical adult patients attending hospital with acute asthma, but the design also means that the study population could have included some patients with other diagnoses. We assessed $MgSO_4$ alongside standard treatment rather than comparing it to elements of standard treatment. This design might have reduced the potential for $MgSO_4$ to make a clinically meaningful difference, but withholding standard treatment would have been unethical. We selected primary outcomes that measured the effect of treatment on symptoms (VAS breathlessness) and management (hospital admission). We also measured physiological parameters and peak expiratory flow rate as secondary outcomes. Other measures, such as forced expiratory volume in 1 s, might have been more sensitive to changes in respiratory function, but these are not routinely measured in the emergency department, and would not provide evidence of clinical effectiveness. Demonstration of clinical effectiveness requires a meaningful improvement in symptoms or management of patients, not just a change in respiratory parameters. Finally, we deliberately excluded patients with life-threatening asthma and were unable to power the study to detect differences in serious adverse outcomes (including death), so we were unable to determine whether $MgSO_4$ has an effect on serious adverse outcomes in life-threatening asthma.

Panel: Research in context

Systematic review

A 2007 systematic review,[10] which was updated in 2009,[12] identified 11 trials of intravenous $MgSO_4$ in 1018 adults and seven trials of nebulised $MgSO_4$ in 430 adults with acute asthma. Meta-analysis suggested that both intravenous and nebulised treatment had potentially worthwhile effects on respiratory function and showed non-significant trends towards reduced rates of admission to hospital.

Interpretation

Our large pragmatic study failed to provide convincing evidence that intravenous or nebulised $MgSO_4$ produce clinically worthwhile benefits in adults with severe acute asthma. Although $MgSO_4$ is a safe treatment with few significant side-effects, current data do not support a role for $MgSO_4$ in the standard treatment of adults with severe acute asthma.

The findings of our trial suggest that there is no role for nebulised $MgSO_4$ in the management of severe acute asthma in adults and at best a limited role for intravenous $MgSO_4$ in this setting. Patients receiving standard treatment had striking improvements in rates of breathlessness and peak expiratory flow, and few required respiratory support. Although most patients were admitted to hospital, nebulised $MgSO_4$ did not reduce the admission rate and we noted only weak evidence of an effect from intravenous $MgSO_4$. The low rate of side-effects and adverse events (other than those related to the underlying illness) suggests a low risk of harm from intravenous administration but the corresponding evidence of benefit is modest and uncertain.

Further clinical trials of $MgSO_4$ in adults with acute asthma are unlikely to be worthwhile. If intravenous treatment has an effect on admission rates or adverse events that was not detected by 3Mg then a much larger trial would be needed to detect such an effect. The logistic barriers to undertaking clinical trials in patients with a medical emergency would seem to prevent a larger trial being feasible at an acceptable cost.

Contributors

The coapplicants (see appendix) designed the trial and developed the research proposal and submitted it for funding. The Project Management Group and Local Investigators undertook the trial with independent oversight from the trial steering committee and data monitoring committee. SG wrote the first draft of the report. MB did the statistical analysis. SG, MB, JC, AG, TC, and JB contributed to redrafting of the paper and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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